SHORT REPORT

Improvement of memory guided saccades in parkinsonian patients by high frequency subthalamic nucleus stimulation

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Abstract
Recent studies in the monkey suggest that the subthalamic nucleus (STN) is involved in control of eye movement, yet its functional significance in humans is unknown. Saccadic eye movements were studied in eight parkinsonian patients treated by bilateral electrical stimulation of the STN. STN stimulation improved the accuracy of memory guided saccades but not of reflexive visually guided saccades and had no effect on the antisaccade task. This study shows that, by contrast with levodopa, STN stimulation improves memory guided saccade deficits, and illustrates for the first time in humans the role of the STN in the control of purposive saccades.
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The role of the subthalamic nucleus (STN) in the control of limb movements is well established. Recent experimental studies suggest that it is also involved in eye movement control.[1] In monkeys, the STN is directly connected with the main frontal ocular motor areas—namely, the frontal eye field[2 3] and the supplementary eye field[4 5] and provides excitatory inputs to the substantia nigra pars reticulata (SNpr). Moreover, the monkey STN contains neurons that discharge during attentive fixation, and neurons with saccade related activity, discharging during memory guided saccades, and visually guided saccades.[1] To investigate the role of the STN in eye movement control in humans, we took the advantage of the presence of electrodes in the STN of patients with Parkinson's disease treated by continuous high frequency stimulation.[6–8] We studied the influence of bilateral STN stimulation on reflexive visually guided saccades, antisaccades, and memory guided saccades in eight patients with severe levodopa responsive Parkinson's disease.

Subjects and methods

Eight patients with idiopathic Parkinson's disease and with bilateral electrodes implanted in the STN were studied (table 1). The delay between surgery and eye movement recordings was 7 (SD 5) months. At that time, all patients had significantly improved clinically (Hoehn and Yahr "off" drug condition=1.7 (SD 0.1) and "on" drug condition=0.8 (SD 0.1) and their drug treatment had been reduced to 545 (SD 105) mg/day (levodopa equivalent dose). Each patient was studied in two sessions in pseudorandom order. In one session ("STN on"), bilateral continuous stimulation was applied to the STN. The electrical parameters were those used chronically to treat the patients: frequency=137 (SD 27.6) Hz, pulse width=58.8 (SD 8.6) µs and voltage=2.4 (SD 0.7) V. In a session performed another day ("STN off"), stimulation was stopped 2 hours before eye movement recordings. In both conditions, levodopa treatment was given 2 hours before eye movement recordings; the patients did not receive anticholinergic drugs. Four patients began by the "STN on" condition and the four others by the "STN off" condition. The patient's motor score (Unified Parkinson's disease rating scale part III) was 10 (SD 7) in the "STN on" condition and 20 (SD 7) in the "STN off" condition.

A control group of 10 subjects (age 53.4 (SD 10) years) without any history of neurological disorders was studied with the same paradigms as the patient group. All subjects gave written informed consent before participation in the

Table 1   Clinical characteristics of parkinsonian patients

Patients	Age (y)	Disease duration (y)	Before surgery		After surgery	
			Hoehn and Yahr (off/on)	Treatment (mg/day)	Hoehn and Yahr (off/on)	Treatment (mg/day)
1	40	15	5/4	1250	1.5/1	1100
2	45	11	5/4	1550	1/0	525
3	50	10	3/1.5	1550	1/0	200
4	54	17	4/2	600	2/1	250
5	65	11	5/2.5	1450	2/1	450
6	46	15	5/3	1500	1.5/1	500
7	59	14	5/1	1575	2.5/1	875
8	61	8	4/2	1750	2/1	475
Mean	52.5	12.6	4.5/2.5	1400	1.7/0.8	545
SEM	3.1	1.1	0.3/0.4	125	0.2/0.2	105

Treatment is expressed in dosage of levodopa equivalent.
Hoehn and Yahr scores were assessed in the "off" and "on" drug conditions.

study, which was approved by the local ethics committee.

Eye movements were recorded using horizontal binocular direct current electrooculography with a sampling frequency of 200 Hz. Visual cues were presented at a distance of 95 cm with red light emitting diodes embedded in a curved ramp (Gaymard *et al*[6]).

REFLEXIVE VISUALLY GUIDED SACCADES
Reflexive visually guided saccades were studied with a gap paradigm. Subjects were instructed to initially fixate a central fixation point that was illuminated for 2.5 to 3.5 seconds, then to make a saccade towards a 25° lateral target that appeared randomly right or left 200 ms (temporal gap) after the extinction of the central fixation point. Saccade latency and saccade gain (saccade amplitude over target amplitude) were measured by averaging values from at least 12 trials in each direction.

Antisaccades
The ability to inhibit reflexive visually guided saccades and to trigger voluntary non-visually guided saccades was tested by the antisaccade task. The same stimulus condition as in the visually guided saccade task was used, but subjects were instructed to look, as quickly as possible, in the direction opposite to the peripheral target (perform an antisaccade) without instructions about saccade amplitude. The result was expressed as percentage of errors by averaging values from at least 18 trials in each direction. Only correct antisaccades were used for the calculation of saccade latency.

Memory guided saccades
Purposive saccades and spatial short term memory were tested by a memory guided saccade task. The central fixation point was initially illuminated for 3 to 4.5 seconds. A 50 ms flash then appeared, randomly right or left, with unpredictable eccentricity (10, 15, 20, 25, or 30°). After the flash, the central fixation point remained illuminated for 7 seconds. The subject was instructed to keep the eyes on the central fixation point during the entire delay, and to trigger a saccade towards the memorised location of the flash as soon as the central fixation point was switched off. Two seconds later, a target with the same location as the flash was illuminated to allow a corrective saccade to be triggered, if necessary. Saccade latency and gain (accuracy) of the initial saccade and of the final eye position (the eye position reached just before the reillumination of the target) were measured by averaging values from at least 25 trials in both directions (Gaymard *et al*[6]). We maintained the attention of the patients by repeating the instruction between the blocks.

The three paradigms were conducted within the same session for all the subjects. The two sessions of the patients ("STN on" and "STN off") were executed in the same conditions with the same number of trials (n=55).

STATISTICS
All variables were checked for significant lateralisations by means of a two tailed Wilcoxon matched pairs signed ranks test, both in patients and controls. In the patient group, this test was used to compare saccade parameters in "STN on" and "STN off" conditions. An analysis of variance (ANOVA) and a *t* test were used for comparisons with the control group. Significance was accepted at a $p<0.05$ level.

Results
As there were no significant differences between rightward and leftward values, all parameters were pooled. Results are presented in table 2. In the gap task, no significant differences in saccade latency or saccade accuracy were found in either group, although saccade latency was longest in the "STN off" condition. Likewise, in the antisaccade task, the percentage of errors was similar in all groups. However, latency of correctly executed antisaccades was significantly increased both in the "STN on" (t =2.12; df =16; $p<0.05$) and "STN off" conditions ($t=3.37$; df=16; $p<0.004$) compared with controls (F (2, 23)=4.95; $p<0.016$). In the memory guided saccade task, saccade latency was significantly increased in the "STN off" condition compared to controls ($t=2.16$; df=16; $p<0.04$). In all tasks, saccade latency was shorter in the "STN on" condition than in the "STN off" condition, but without reaching significance. Saccade accuracy was similar in the "STN on" condition and controls. However, in the "STN off" condition, first saccade gain was significantly decreased compared with that of the "STN on" condition ($Z=-2.52$; n=8; $p<0.01$) and controls (F (2, 23)=-3.56; $p<0.04$, figure) and also significantly decreased compared with the final eye position gain ($Z=-2.38$; n=8; $p<0.01$). In the "STN off" condition, accuracy of final eye position showed only a partial improvement, remaining slightly but significantly decreased compared with that of the "STN on" condition (Z =-1.96; n=8; $p<0.049$).

Table 2   Saccade parameters

	Visually guided saccades		Antisaccades		Memory guided saccades		
	Latency (ms) Mean (SD)	Gain Mean (SD)	Latency (ms) Mean (SD)	% Errors Mean (range)	Latency (ms) Mean (SD)	First gain Mean (SD)	Final gain Mean (SD)
Patients:			⋆				
STN on	201 (45)	0.95 (0.03)	347 (85)	6.6 (0–29)	385 (68)	0.91 (0.12)	0.95 (0.09)
			⋆⋆		⋆	††⋆	†‡‡
STN off	220 (71)	0.94 (0.04)	382 (75)	7.7 (0–29)	406 (80)	0.77 (0.19)	0.87 (0.15)
Controls	180 (44)	0.94 (0.02)	278 (70)	7 (0–17)	332 (65)	0.91 (0.04)	0.92 (0.06)

Comparison with the control group: *p<0.05; **(p<0.01). Comparison between "STN on" and "STN off" conditions in PD patients: †p<0.05; ††p<0.001. Comparison between the first gain and the final gain ‡‡(p<0.01).
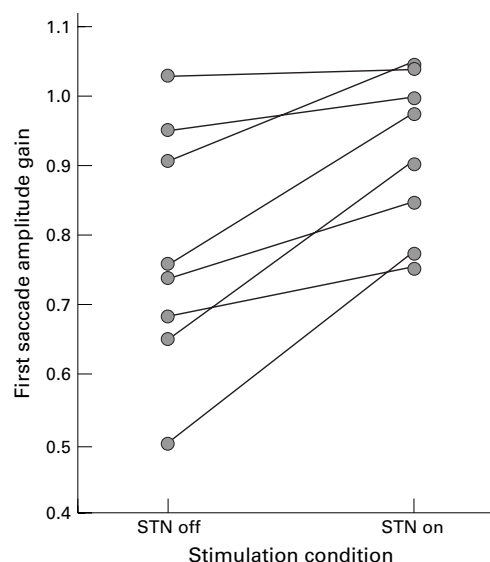
Accuracy of memory guided saccades. The circles represent mean amplitude gain of a patient without STN stimulation ("STN off") and with STN stimulation ("STN on"). We noted an improvement in each case.

Discussion

Patients with Parkinson's disease have a significant deficit in accuracy of memory guided saccades.[10–12] Levodopa treatment has no effect on this deficit,[13] suggesting additional dysfunction of non-dopaminergic neuronal systems in this disorder. We found that, by contrast with levodopa, bilateral stimulation applied to the STN reduces this impairment. The observed inaccuracy of memory guided saccades in the "STN off" condition seems to be due to motor as well as to mnemonic deficits as both first gain and final eye position were clearly abnormal, although a slight improvement between first gain and final eye position was seen. The inaccuracy of final eye position does not seem to be due either to the effects of surgical intervention or to those of deep brain stimulation.[14 15] On the other hand, in the "STN on" condition, first gain and final eye position were normal, suggesting that STN stimulation acts both on motor and mnemonic components of memory guided saccades. Another study has shown that in parkinsonian patients final eye position was normal although initial saccade gain was reduced, but the memorisation delay was 5 seconds instead of 7 seconds in our study; this could partially explain the difference in the accuracy of final eye position.[16]

Effects on the motor component of volitional saccades could be mediated through direct connections between STN and SNpr, modulating tonic inhibitory SNpr outputs on the superior colliculus, ocular motor structures located between the frontal eye field and superior colliculus.[3 17] This hypothesis is further substantiated as STN and SNpr neurons show saccade related activity during execution of memory guided saccades.[1 17] During the memory delay of a memory guided saccade task, neurons in STN and dorsolateral prefrontal cortex (DLPFC) show spatially selective activity.[1 18 19] In the DLPFC, this activity is thought to represent a probable correlate of spatial short term memory.[18 19] Functionally, a close relation between these two areas is supported by the finding of increased cerebral blood flow in the DLPFC during STN stimulation in patients performing hand movements.[7] It seems therefore plausible to hypothesise that improvement of the mnemonic component of memory guided saccades in our patients was related to modulation of neuronal activity in the DLPFC by STN stimulation.

STN stimulation is effective in reducing parkinsonian motor symptoms such as akinesia, rigidity, and tremor.[6] Although the exact mechanism of STN stimulation is still not known, it may act by an inactivation of increased burst activity of STN neurons due to lack of dopamine in the striatum.[8] Stimulation of the STN improves levodopa sensitive symptoms, but evidence for effects on levodopa resistant symptoms has been lacking so far.[6] Here, we show the efficacy of STN stimulation on a Parkinson's disease deficit resistant to levodopa. Thus our results suggest that the neuronal effects of STN stimulation corrects abnormal activities of the STN which are not due solely to the dopamine deficiency.

In conclusion, our data show that, by contrast with levodopa, continuous high frequency stimulation of the STN improves eye movement deficits seen in patients with Parkinson's disease. This is the first evidence for a significant role of the human STN in the control of purposive saccades, a result that is consistent with its location on frontal efferent ocular motor pathways.

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NEUROLOGICAL STAMP

Neurological truant

The eminent surgeon Lord Moynihan picturesquely described those qualified in medicine but who abandoned the profession to take up pure science, literature, politics, etc, or who studied medicine only for a time as "truants from medicine". Professor Ivan Donaldson, a New Zealand neurologist, has combined truancy with neurological practice. With his family Ivan Donaldson has established a nationally famous vineyard. The very high quality wine has led to the vineyard being portrayed on a stamp and in so doing Ivan Donaldson is probably the only neurological vigneron who has been philatelically honoured.

Two or three glasses of wine daily have been found to reduce deaths from coronary and cardiovascular disease by 35%, and two glasses of wine a day diminish deaths from cancer by 22%. Although mortality from all causes is reduced by 30% by moderate amounts of wine, it increases again when drinking more than seven glasses daily with a glass judged to contain 120 ml.[1] Wine may also reduce the incidence of dementia.[2] Assuming moderation by imbibers, Professor Ivan Donaldson may be responsible more than any other neurologist for protecting the brain from at least two ominous threats of advancing age.

This stamp shows part of Dr Donaldson's 80 acre vineyard situated in Waipara some 35 miles north of the city of Christchurch in the South Island of New Zealand. In the

foreground left is a bunch of grapes and on the right is one of Professor Donaldson's sons (Stanley Gibbons 2060, Scott 1432).

L F HAAS

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